

Palladium-Catalyzed Coupling of Terminal Alkynes to the Free *cis*-Diol Metabolite Produced from the Oxidation of Bromobenzene by *Pseudomonas putida*: Synthesis of New Homochiral 3-Alkynyl *cis*-Cyclohexa-3,5-diene-1,2-diols

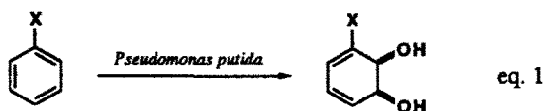
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(Received 5 December 1991)

Abstract: The free *cis*-diol metabolite (1) produced from the oxidation of bromobenzene by *Pseudomonas putida* underwent Pd(0)-catalyzed coupling with trimethylsilyl acetylene, phenylacetylene and 1-hexyne providing the novel homochiral (1*S*, 2*R*)-3-alkynyl *cis*-cyclohexa-3,5-diene-1,2-diols 2-4 in good to excellent yields.

The microbial oxidation of substituted benzenes by mutant strains of *Pseudomonas putida* to produce 3-substituted *cis*-cyclohexa-3,5-diene-1,2-diols (eq. 1)¹ has provided a powerful means for obtaining homochiral synthons useful in the preparation of a variety of important medicinals and naturally occurring substances.² The significance of the benzene

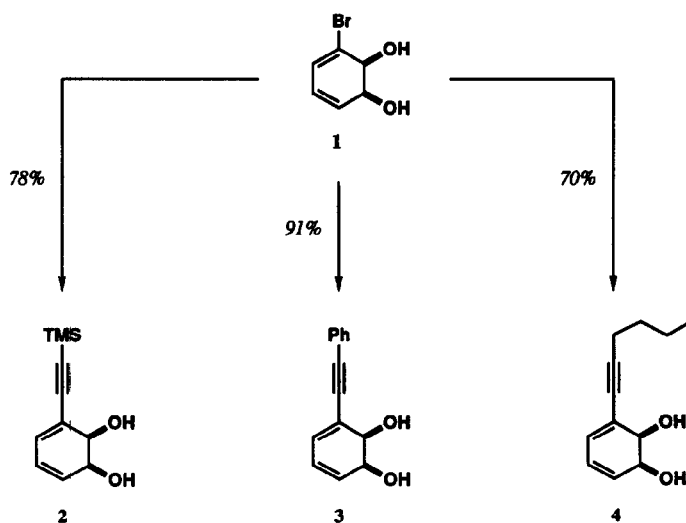


substituent (X) lies in its directing the stereoselectivity of the enzymatic oxidation. Although a number of substituted benzenes serve as substrates for the dioxygenase,³ only a limited number of substituents (X = halogen, methyl, vinyl) allow for diol production in reasonable quantities (>1 g/L of culture).

We have been interested in achieving carbon-carbon bond forming reactions at the brominated carbon atom of the free diol **1** since this would allow for the synthesis of 3-substituted *cis*-cyclohexa-3,5-diene-1,2-diols not otherwise accessible in reasonable quantities by microbial oxidation.⁴ In addition, a successful carbon coupling reaction performed on the *free diol* would allow for regioselective hydroxy group substitution^{2b,5} (as opposed to diol protection) immediately following the carbon-carbon bond forming step.

The mild conditions employed in the palladium mediated coupling of terminal acetylenes to vinyl halides ($\text{Pd}(\text{PPh}_3)_4 / \text{CuI} / \text{nBuNH}_2$)⁶ seemed a viable means for achieving this objective. We are pleased to report that under these conditions, the bromodiol **1** underwent smooth coupling with trimethylsilyl acetylene, phenyl acetylene and 1-hexyne to provide the novel 3-alkynyl *cis*-cyclohexa-3,5-diene-1,2-diols **2–4** in good to excellent yields⁷ (Scheme I).

Scheme I



The synthesis of **2** is typical of the method employed: to a stirred mixture of $\text{Pd}(\text{PPh}_3)_4$ (107 mg, 0.093 mmol), CuI (23 mg, 0.12 mmol) and diol **1** (300 mg, 1.57 mmol) was added benzene (2 ml) followed by neat nBuNH_2 (176 mg, 2.41 mmol) and the

slow dropwise addition of a solution of trimethylsilyl acetylene (163 mg, 1.66 mmol) in benzene (0.5 ml). The resulting solution was stirred at rt for 2 h and then diluted with EtOAc (10 ml). The organic layer was washed with sat. NH₄Cl (2 x 5 ml) and brine (1 x 5 ml) and dried over Na₂SO₄. Filtration and concentration *in vacuo* provided a crude solid which was purified by flash chromatography on silica gel (deactivated with 10% by weight water) eluting with 2:1 hexanes / EtOAc. The pure diol **2** was obtained as a white solid (255 mg, 1.22 mmol, 78% yield, [α]_D = +186, *c* = 1.77, CHCl₃). Alternatively, the reaction mixture may be partially concentrated *in vacuo* and immediately subjected to flash chromatography without workup. By this method, the pure diols **3** ([α]_D = +181, *c* = 1.11, CHCl₃) and **4** ([α]_D = +144, *c* = 1.54, CHCl₃) were isolated in 91% and 70% yields respectively.

The work reported herein illustrates an additional versatility of the bromodiol **1** as a chiral synthon through its ready conversion to a variety of alkynyl substituted arene *cis*-diols that may not otherwise be obtained in a practical manner by microbial oxidation. Methods for coupling additional types of functionality to **1** and its derivatives are currently under investigation.

Acknowledgements

This work was supported by the National Institutes of Health, the Jeffress Trust Fund and TDC Research Inc. The authors thank Dr. Christie H. Boros for obtaining the ¹³C NMR (DEPT) data on **2-4**.

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